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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,680	12/08/2000	Martin Adamczewski	Mo-6000/LcA 34,147	2900

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	//

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,680	ADAMCZEWSKI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 10 on 5/2/02. Applicant's election without traverse of group VI, drawn to methods of screening compounds which alter the conductive properties of acetylcholine receptors, is acknowledged. Claims 23-41 and 44 were canceled, and claim 45 was added as requested. Claims 42, 43, and 45 are pending and under consideration in this Office Action.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **At page 14, lines 18 and 19, nucleic acid sequences are disclosed which are in excess of 10 bases, but which lack any SEQ ID NO.** These sequences are similar, but not identical, to SEQ ID NOS:3 and 4. The sequences at page 14 differ in that they comprise inosine residues. These sequences must be disclosed in the Sequence Listing.

Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Objections

Claim 42 is objected to because, as amended, it is drawn to non-elected subject matter. Applicant elected without traverse in Paper No. 10 methods of screening compounds which alter the conductive properties of acetylcholine receptors. Claims 42 has been amended to encompass methods of screening compounds that alter **at least one property** of an acetylcholine receptor, and therefore embraces receptor properties other than conductivity. This material is beyond the scope of the elected invention. Claim 43 has been amended, therefore they embrace non-elected

subject matter. Applicant is required to amend or cancel claims drawn to non-elected subject matter, pursuant to 37 CFR 1.145. **The scope of material under consideration in this Office Action is limited to methods of screening compounds which alter the conductive properties of acetylcholine receptors, and to methods of identifying compounds that bound to an acetylcholine receptor.**

Claim 42 is objected to because it is ungrammatical. Specifically, it lacks proper subject verb agreement between the subject "sequences" and the verb "alters". See lines 7 and 9 of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 42, 43, and 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 25.

Claims 42 and 45 are drawn to methods of screening compounds which alter the conductive properties of acetylcholine receptors. Claim 43 is drawn to a method of identifying

compounds that bind to an acetylcholine receptor. The methods employ nucleic acids from the following group:

-nucleic acids consisting of SEQ ID NO:1;

-subsequences of SEQ ID NO:1 at least 14 bases in length;

-sequences that hybridize with SEQ ID NO:1

-sequences that are 70% identical to bases 43-1368 of SEQ ID NO:1;

-sequences complementary to SEQ ID NO:1;

-sequences which encode any of the amino acid sequences encoded by the sequences above;

-sequences that encode a polypeptide that functions as an acetylcholine receptor beta subunit in which causes a change in a conductive property of an acetylcholine receptor, and which is at least 40% identical to SEQ ID NO:2.

Embodiments of claim 45 employs the polypeptides encoded by the nucleic acids set forth above.

The first of these groups of nucleic acids is drawn to a species, nucleic acids consisting of SEQ ID NO:1, which is fully disclosed and adequately described. Similarly the polypeptide of SEQ ID NO:2 is fully disclosed and adequately described. The remaining groups of sequences represent genuses. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by

complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic.

In order to function as intended in the method, all of the nucleic acid sequences must encode an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor with conductivity properties. The specification describes by complete structure no amino acid sequence, other than SEQ ID NO:2, that fulfills this functional requirement. Neither is any relevant identifying characteristic described, such as a correlation between a specific structure and the required function. The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. In this case, hybridization characteristics and percent homology give no insight as to the functional charcateristics of the encoded polyepetides. It is not sufficient to define a nucleic acid or polypeptide solely by its principal biological property, e.g., an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor, because an alleged conception having no more specificity than that is

simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for an acetylcholine receptor beta subunit which can be assembled into a functional acetylcholine receptor. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). Because, there is disclosure of only a single member of the claimed genuses, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Enablement

Claims 42, 43, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening compounds which alter the conductive properties of acetylcholine receptors, or which bind to acetylcholine receptors, wherein the methods require a nucleic acid encoding SEQ ID NO:2, or subsequences of SEQ ID NO:2 that can be assembled into a functional acetylcholine receptor, or wherein the methods require the polypeptide of SEQ ID NO:2 or subsequences of SEQ ID NO:2, does not reasonably provide enablement for a such methods that employ subsequences of SEQ ID NO:1 that are only 14 bases in length, or that employ nucleic acid sequences encoding polypeptides that differ from the entire sequence of SEQ ID NO:2 or from subsequences of SEQ ID NO:2, or for methods that employ variants of SEQ ID NO:2 or variants of its subsequences. Nor does the specification enable compounds useful for either or both of crop protection and pharmaceutical treatment of humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As discussed above under Written Description, in order to function in the claimed invention, the recited polynucleotides must encode polypeptides that can be assembled into a functional acetylcholine receptor with conductivity properties. The specification discloses an assay which can be used to measure conductivity, but discloses only a single polypeptide that will function in the claimed invention. It is considered to be routine in the art to perform terminal

deletions of nucleic acids in order to determine what is the minimal functional encoded polypeptide. However, because acetylcholine receptor beta subunits generally have four transmembrane domains and a ligand binding site (Bossy et al EMBO J. 7(3): 611-618, see e.g. Fig. 3), it is unrealistic to assume that a nucleic acid of only 14 nucleotides could encode a polypeptide that could fulfill the function of an acetylcholine receptor beta subunit. At a minimum, the role of the beta subunit in conductivity is to form part of the membrane channel. One of ordinary skill in the art appreciates that it takes about 18-20 amino acids to form a single transmembrane domain. Clearly nucleic acids segments as short as 14 bases cannot encode a polypeptide with this function, and would be inoperable in the invention.

The claims also explicitly contemplate using polypeptides encoded by the complement to SEQ ID NO:1. Neither the specification nor the prior art of record provide any reason to believe that the complement of SEQ ID NO:1 encodes any polypeptide which would function as a acetylcholine receptor beta subunit.

Turning now to nucleic acids that encode variants of SEQ ID NO:2 or its subsequences, the specification fails to provide an enabling disclosure because it fails to teach which variants will provide a functional beta subunits, and which will not. The claims embrace nucleic acids that hybridize to SEQ ID NO:1, nucleic acids that are only 70% identical to SEQ ID NO:1 or its subsequences, and nucleic acids encoding polypeptides that are only 40% identical to SEQ ID NO:2. Guidance in the specification as to which variants will provide a functional beta subunit is limited to a discussion of which amino acid substitutions constitute conservative substitutions.

See pages 8 and 9. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". Applicant has provided little or no guidance to enable one of skill in the art to determine, without undue experimentation, the positions in the claimed nucleic acids which are tolerant to change, and the nature and extent to of changes that can be made in these positions in order to retain function as required by the claims. Even if critical residues were identified in the specification, which they are not, the mere identification of these residues as critical would not be sufficient, as

the skilled artisan would immediately recognize that critical sites must assume the proper three-dimensional configuration to be active, and that conformation is dependent on surrounding residues as well. Thus alterations in sequences which are not apparently part of a binding site can destroy activity by altering the overall conformation of a protein. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will eliminate receptor function, and which will be tolerated as required by the claims, and no such guidance is available in the art of record. In the absence of such guidance or examples, and in view of the unpredictability of the subject matter and the breadth of the claims, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Similarly , the specification fails to provide an enabling disclosure because it fails to teach which compounds that bind to acetylcholine receptors or alter their conductivity are useful

for either or both of crop protection and pharmaceutical treatment of humans. The breadth of the crops which may be protected, and the diseases from which they may be protected, is not limited by the specification. Also the breadth of pharmaceutical treatments of humans is not limited. The specification provides no guidance or examples whatsoever in this regard. Again, one might argue that one could determine empirically which compounds that bind and/or alter receptor conductivity will be useful for crop protection or pharmaceutical use. However, as noted above, compliance with 35 USC 112, first paragraph requires that one must be able to resort to known scientific laws to predict the performance characteristics of inventions. The specification provides no way to predict which compounds will be useful for the intended purposes. Also absent is any guidance regarding dosages of compounds for treatment or protection against any pathogen, nor is there any guidance with respect administration routes and profiles. Furthermore such issues as bioavailability, toxicity, pharmacokinetics, drug metabolism and clearance, and the age, health, sex, and species of patient, all of which must be considered int he course of drug development and use, are not addressed in the specification.

The specification also fails to provide an enabling disclosure because essential elements of the invention are incorporated by reference to a non-patent publication. Specifically, the claims recite the limitations of "70% identity" to the sequence between position 43 and 1368 of SEQ ID NO:1, and "40% identity" to SEQ I D NO:2. Guidance in the specification as to how to calculate these identities is found at page 4, lines 29-31 and page 6, lines 26-28, which passages suggest use of GCG program GAP, version 10.0, using "the standard settings". The standard

settings are attributed to Devereux (1984). Because the value of sequence identity obtained using this program depends on the value of user-adjustable parameters, the specification must identify exactly what parameters to use. The identities of these parameters represent essential elements of the invention inasmuch as they define its metes and bounds. In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See MPEP 608.01(p), and In re Fouche, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42, 43, and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42, 43, and 45 are indefinite because they recite "the biological function of an acetylcholine receptor" without antecedent basis. Acetylcholine receptors can be viewed as having several biological functions including, at least, ligand binding and channel formation. The claim fails to stipulate what biological function is intended.

These claims are also indefinite because it is unclear what are the metes and bounds of

Claims 42, 43, and 45 are indefinite because they recite "the sequence between position 43 and 1368 of SEQ ID NO:1" without antecedent basis. There are many sequences between positions 43 and 1368 of SEQ ID NO:1, it is unclear to which sequence Applicant refers. Substitution of "the sequence comprising positions 43-1368 of SEQ ID NO:1" for "the sequence between position 43 and 1368 of SEQ ID NO:1", is suggested.

Claims 42, 43, and 45 are indefinite because it is unclear what is intended by "70% identity" or by "40% identity". The specification teaches that preferably identity is calculated using of GCG program GAP, version 10.0, using "the standard settings". However, one of skill in the art appreciates that there are other available programs which may be used, and that there are a variety user-chosen parameters which may be varied, and that the calculated identity will vary with the program and the parameter values chosen. Because the claims fail to set forth the program and parameter values used in the calculation, one cannot know what is intended by either "70% identical" or "40% identical".

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER